A review on potential toxicity of dental material and screening their biocompatibility

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Abstract: OBJECTIVES A wide range of compounds are utilized in dentistry such as dental composites, resins, and implants. The successful clinical use of dental materials relies on theirm physiochemical properties as well as biological and toxicological reliability. Different local and systemic toxicities of dental materials have been reported. Placement of these materials in oral cavity for a long time period might yield unwanted reactions. An extensive variety of materials is used in dentistry including filling materials, restorative materials, intracanal medicines, prosthetic materials, different types of implants, liners, and irrigants. The increasing rate in development of the novel materials with applications in the dental field has led to an increased consciousness of the biological risks and tempting restrictions of these materials. The biocompatibility of a biomaterial used for the replacement or filling of biological tissue such as teeth always had a high concern within the health care disciplines for patients. MATERIALS AND METHODS Any material used in humans should be tested before clinical application. There are many tests evaluating biocompatibility of these materials at the point of in vitro, in vivo, and clinical investigations. RESULTS The current review discusses the potential toxicity of dental material and screening of their biocompatibility. CLINICAL RELEVANCE It is essential to use healthy and safe materials medical approaches. In dentistry, application of different materials in long-term oral usage demands low or nontoxic agents gains importance for both patients and the staff. Furthermore, screening tests should evaluate any potential toxicity before clinical application.

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A review on potential toxicity of dental material and screening their biocompatibility

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Short title: *Biocompatibility and toxicity of dental materials*

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Abstract

Objectives: A wide range of compounds are utilized in dentistry such as dental composites, resins and implants. The successful clinical use of dental materials rely on their physiochemical properties as well as biological and toxicological reliability. Different local and systemic toxicities of dental materials have been reported. Placement of these materials in oral cavity for a long time period might yield in unwanted reactions. An extensive variety of materials is used in dentistry including filling materials, restorative materials, intracanal medicines, prosthetic materials, different types of implants, liners and irrigants. The increasing rate in development of the novel materials with applications in the dental field has led to an increased consciousness of the biological risks and tempting restrictions of these materials. The biocompatibility of a biomaterial used for the replacement or filling of biological tissue like teeth always had a high concern within the health care disciplines for patients. **Materials and Methods:** Any material used in humans should be tested before clinical application. There are many tests evaluating biocompatibility of these materials at the point of in vitro, in vivo and clinical investigations. **Results:** The current review discusses the potential toxicity of dental material and screening of their biocompatibility. **Clinical Relevance:** It is essential to use healthy and safe materials medical approaches. In dentistry, application of different material in long-term oral usage demands low or non-toxic agents gains importance for both patients and the staff. Furthermore, screening tests should evaluate any potential toxicity before clinical application.

Keywords Biocompatibility ● Composite resin ● Dentin ● Dentistry ● Dental materials ● Toxicity

Introduction

There are some different descriptions for biocompatibility in the literature. However, in general it refers to the ability of a material to produce an suitable host response when applied as intended [1]. Evidently, biocompatibility can define as the compatibility of a material with a living tissue/system by not being toxic, harmful, physiologically reactive or including immunological rejection [2, 3]. In addition, Based on biocompatibility (the reaction of the tissue to the used biomaterial), dental used biomaterials can be classified as biotolerant, bioinert and bioactive. The examples for these classes are summarized in Table 1.

An extensive variety of materials are used in dentistry including filling materials (such as composites, amalgam, polymeric monomers, cements), restorative materials, intracanal medicines, prosthetic materials, different types of implants (pure titanium, **Titanium** alloys, Zirconium), liners, irrigants, as well as mouthwash (such as antiseptic and anti-plaque rinse) [4-7]. The increasing rate in development of the novel materials with dentistry applications has led to an increased consciousness of the biological risks and tempting restrictions of these materials. The biocompatibility of a biomaterial used for the replacement or filling of biological tissue like teeth always had a high concern within the health care disciplines for patients. On the other hand, dental staff are also at risk of adverse effects to the some biomaterials. With some biomaterials, the risks are even higher for staff than patients. For instance, dental resins or rubber products may result to adverse reactions to dental staff such as hand and fingertip reactions [8]. Some reports have also shown generalized neuropathy after fourteen years of contact and exposure to methacrylates for dental staff [9].

Biological and immunological adverse reactions have reported to dental materials are infrequent and the reported side effects are not severe. However, this completely depends on the kind of the materials used and the technique used by staff. In some rare cases severe reactions have been published. Mjor reviewed the problems and benefits of dental restorative materials and their adverse effects. He emphasized that the allergic reactions are the most confirmed side effects to dental materials due to their known allergen

components like transition metals and solutions such as formaldehyde [10]. Formaldehyde may form as by-product of unreacted monomers from some dental resins that may lead to even enhanced tissue responses [11]. Dental amalgam is a mixture of liquid mercury and metal alloy that used in dentistry to fill cavities caused by tooth decay [12]. The cellular and molecular toxicities of mercury as the main component of amalgam is pictured in figure 1. Criticizers claimed that it has toxic effects that convert it to unsafe, both for the patient and staff. They argued that it perhaps show even more toxic effects for the dental staff operating it during a restoration [13]. Skin and mucosal reactions are reported as the main biological adverse effects associated with dental materials [14]. Figure 1

In general, dental materials are used for replacing damaged or defective dental tissues, and so, they should be chemically stable and inert for the oral cavity. However, as we know all materials show some degree of dissolution or degradation. Then, when the dissolved components from a material is toxic, the local or systemic reactions are probable. Therefore, due to the long-term utilization and durability of dental materials in the oral cavity as well as their contact or exposure with dental staff, there is a real need to ensure their biocompatibility. In this paper, a brief overview was performed on the toxicity and biocompatibility of different materials used in dentistry.

Toxicity of dental materials

Since dental materials are directly in touch with oral cavity, it's crucial to have a comprehensive understanding of the biocompatibility, toxicity and physiochemical properties of material used in dentistry. The plausible cytotoxicity of different dental materials will be presented below.

Replacing the inorganic structure in dental tissue with resins is the initial purpose in application of adhesive systems [15]. The classification of adhesive systems were based on their link with smear layer whereas it is nowadays categorized according to the stages in clinical usage called total-etched and self-etched adhesive

methods. Some dental adhesives are not polymerized, instead they are degraded and separated from resins and form free radicals which are provocative agents in induction of toxicity [16].

Methacryloyloxy-dodecyl-pyridinium bromide as an important part of adhesive resins has been shown to trigger toxicity at high concentrations, although in lower concentration the antibacterial effects have been reported. Easy liberation of polymer followed by increased diffusion my stand for unwanted biological reaction [17, 18]. In addition, defective polymerization of free resin monomers and dissolutions with saliva or food intake within the first 24h can give rise to cytotoxic effects on pulp tissue. Immunosuppression, mild to severe inflammation of pulp tissue and apoptotic cell death are the detrimental effects of adhesive resins previously reported [19, 20]. For instance, bisglycidylmethacrylate (Bis-GMA), hydroxyethylmethacrylate (HEMA), urethanedimethacrylate (UDMA), triethyleneglycoldimethacrylate (TEGDMA) caused cytotoxicity in mouse fibroblasts after 24-72 h post exposure in which the mechanism of toxicity were mitochondrial malfunction and expression of inflammatory mediators [21].

The cytotoxic free monomers are also appropriate surface for cariogenic microorganisms. It has been stated that these monomers stimulate the growth of cariogenic bacteria such as Streptococcus. Sobrinus and Lactobacillus acidophilus of TEGDMA. Besides, TEGDMA promotes proliferation of Streptococcus mutans and Streptococcus salivarius. These microorganisms have vital role in dental caries and initiate cellular mechanisms involved in pulp damages and allergic reactions [22-24]. Besides, resins result in the expression of cascades of proteins involved in the inflammatory reactions. This is in tight connection with allergic reactions such as eczema-like skin symptoms. In addition, high concentrations of these materials may display sub-acute and chronic toxicities which can show noxious effects in different body organs [25, 26].

Oral soft tissue damages such as gingivitis are among the different reactions following the application of restorative materials. Regarding *in vivo* toxicity screenings of restorative materials, it is not unequivocally understood that the cytotoxicity is a result of materials or the bacterial plaque accumulated on the teeth [27].

The cytotoxicity related to cement usage has been shown to significantly decrease in time. This effect is attributed to the buffering impact of the saliva and present proteins [28]. Moreover, similar results have been observed in the toxic effects of composites in fibroblasts *in vitro* which was shown to substantially decrease in aged composite models in artificial saliva [29]. However, some *in vivo* experiments pose the safety and biocompatibility of the applied composites. Ponce-Bravo et al examined the sub-chronic toxicity of commercial MEDENTAL Light-Cure Composite in rats. The results indicated that no cytological changes in microscopic and also hematological tests were observed [30].

Although composite resin materials exhibit clinical advantages due to their physicochemical specifications, induction of some toxicities may constrict their application. In a study conducted by Şişman the cytotoxicity of five bulk fill composite resins, Filtek Bulk Fill, Tetric EvoCeram Bulk Fil, Sonic Fill, X-trafil and SDR were tested in human dental pulp stem cells. The results of this study showed that the viability of the cells in WST-1 assay was plunged during the incubation period [31].

In summary the mechanism of toxicity have been proposed to be related to short-term release of free monomers as well as long-term liberation of leachable components as a result of degradations over time. Additionally, ion release and growth of microorganisms in the interfacing location of teeth and dental materials are involved in the tissue damages occurring in situ. Productions of reactive oxygen species and depletion of cellular glutathione reservoirs are molecular mechanisms of probable pulp and gingival apoptosis implicated in resin monomers and also restorative material based-toxicities. Some additives to dental resins are potential substrates for cariogenic bacterial strains which can lead to subsequent secondary caries and degradation of the polymers lasting in the failure of the restoration [29].

In spite of the widespread use of alloys as casting materials, their toxicological profile is not comprehensively determined yet. Controversial results have been obtained after several tests studying their biological safety [32]. The application of nano-silver materials in accordance with dental alloys has gained increasing

momentum at the same time since they possess both antimicrobial and anti-inflammatory properties [33]. However, silver nanoparticles have been reported to induce cytotoxicity via interfering with different signaling pathways [34]. A novel 3D culture in LOD2 cells which resemble an *in vivo*-like environment assessed the toxicity of dental castings coated with silver nanoparticle. Cell viability tests revealed the materials have a time-dependent toxicity [35].

Moreover, other metal-based alloys such as Cu-based alloy (Thermobond), Ni-Cr alloys (Remanium CS, Heranium NA, Wiron 99, CB Soft) and Co-Cr alloy (Wirobond C) used commercially have been stated to cause toxicity *in vitro* in which Cu ions have more detrimental effects in cell viability. However, Bioherador N alloy had meaningfully less cytotoxicity than the other ones [36].

There are other dental materials which cause toxicity needing cautions prior usage. For instance, in pediatric dentistry, eugenol combined with zinc oxide which is a root canal sealer in pulpectomy has been reported to induce toxicity [37]. Also, in combination with carvacol and thymol is used to prohibit the proliferation of fungal infections [38-40]. Disruption of cellular plasma membrane, interfering with ion homeostasis and induction of oxidative stress are the proposed mechanisms implied with eugenol application [41, 42]. Furthermore, eugenol has been reported to induce antiplatelet activity through inhibition of cyclooxygenase 2 enzyme in human [43]. Eugenol, in a concentration dependent manner, is capable in cytotoxicity induction in dental pulp fibroblasts of primary teeth [44].

Replacement of missing teeth via implants, have made them reliable treatment surrogate in dentistry [45]. The physical and chemical properties of implant material should encompass well biocompatibility, resistance and strength specifications [46, 47]. In addition to implants, there are several materials used for implant coatings which affect the efficiency of clinical application. These materials should also be examined for any toxic effects to obtain successful impacts in practice [48].

In a study conducted by Reigosa et al, the cytotoxicity and genotoxicity of current titanium based-implants was investigated in osteoblast cells. According to the results of neutral red uptake test, alkaline phosphatase enzyme activity and lysosomal stability tests no significant cytotoxicity was reported in the applied implants. Also comet assay outcomes did not encounter any genotoxicity [49]. However, a systematic toxicity assessment at every stage of testing, through *in vitro* to *in vivo*, is critical to warrant a longer implant lifetime [50].

Titanium and zirconium are the most preferred choices for dental implants by way of they known as inert materials. However, in some cases they may also encourage toxic effects that even might be responsible for the implant failure. They are very reactive metals and then with exposing to oral fluid or air they rapidly form a oxide layer. Then, titanium dioxide (TiO_2) or zirconium dioxide (ZrO_2) can act a boundary at the interface between the oral medium and the metal structure. Any separation of the oxide layer may lead to corrosion of these metals and release of them into oral cavity [51-53]. Besides, this process may also cause to collection of titanium/zirconium ions in tissues especially local lymph nodes, and pulmonary tissue. Collection of titanium particles inside the macrophage lysosomes have reported to show hypersensitivity reactions [54]. In an implant failure study by Frisken et al, two implants egress without any infection, and the existence of titanium in the lungs was observed to be 2.2–3.8 times higher than normal [55].

Coating of bioinert materials with ability to encourage osseointegration on the titanium implant surfaces in order to improve the stability of them has been reported by different investigators [7, 56]. Based on the related literature, different types of biomaterials have used as particle coatings to the dental implant surface to progress soft tissue integration and therefore enhance dental implants success. In recent years, that types of nanoparticles with ability to induce a chemical bond with bone to advantage an ideal biological fixation are applied as coating of dental implants. Indeed, investigators attempt to improve bone incorporation of dental implants using nanoparticles as dental implant coatings. However, the same properties of nanoparticles that

may progress the functionality may also display some unknown adverse effects, such as instability because of nano-coating or cellular nano-toxicity. The understanding of probable cellular effects and toxicity of nanoparticles as well as their environmental effects is necessary in this regards[57].

The implant insertion may also expose in risk to bacterial plaque [7, 56]. The reports have shown that dental implants are at an enlarged risk of microbial contamination due to continuously colonization of microorganisms in the oral cavity. Furthermore, owing to the limited blood supply of peri-implant tissues as well as the lack of periodontal space at the implant–tissue interface, susceptibility of infection is increased in the interface [58]. The formation of infection is introduced by oral streptococci and followed by other microorganisms [59]. Then, it slowly leads to accumulation of anaerobic bacteria [60] that may cause the resorption of circumfluent bone and so may result in implant failing [61]. Nanoparticles have also recognized as one of the most effective antibacterial agents in different fields. Surface modification of titanium using antibacterial possessions of metal nanoparticles can decrease the number of bacteria and positively show more helpful clinical treatments. However, the unknown cellular effects of them are yet in challenge. Coating of implants by metal and metal oxide nanoparticles may leads to toxicity at higher concentrations of them due to ion release process. This outcome can be high risk both for patient and staff [62].

Allergic reactions

Non-biocompatible dental materials might cause different tissue responses, such as local or systemic toxicity and hypersensitivity reactions. Allergic reactions as alarming common public health problems are daily increasing in patients using different materials since they remain in the oral cavity for a long time [63].The first reported allergic reaction occurred in amalgam application in 1928 [64]. The extent of allergic reactions might be low with clinical manifestations such as urticarial, rash and swelling. However, it can cause life threatening side effects which indicated the importance of the issue [65]. In the oral cavity T-cell-mediated hypersensitivity reactions can result in mucosa damage, stomatitis and cheilitis [63]. Search of literature reveals that amalgam

has a robust causative role in induction of toxicity leading to oral lichenoid reactions in comparison to other materials [66]. Due to the raised number of patients with allergies it is important to have adequate knowledge in this issue.

Allergic response to implants arises from the metal ion release or from implant corrosion procedure. The released ions may lead to complex formation with proteins and as allergens producing hypersensitivity responses [67]. The allergic reaction that have observed with titanium implants include edema, redness, urticaria, eczema and pruritus of the skin or mucosa [67]. It has also reported that the risk of titanium allergy in patients who show sensitivity to other metals is more predominant. The allergic reactions related to implants have observed to display more serious problems in some cases with the signing of atopic dermatitis, impaired healing of fractures, pain, necrosis, and tolerance that leads to failing of implant [68].

Genotoxicity

Induction of DNA damage via an agent is referred to the genotoxic effects of the chemical. Due to the reciprocal relationship between genotoxicity and carcinogenesis, it is necessary to clarify the potential genotoxic effects of dental materials for both patients and staff health care. It is worth to include again that many of these materials remain for long periods in the mouth. The genotoxic effects of distinct dental material like bleaching agents is vivid, since it contains hydrogen peroxide. The occurrence of oxidative stress via the increment of oxidizing agents intimately induces DNA damage and mutations [69, 70]. The commercial products of dental bleaching agents have been shown Genotoxicity in Chinese hamster's ovary and mouse lymphoma cells [71, 72]. Also, toothpastes comprising whitening agents have been proved to exert genetic damages in human gingival cells [73]. Dental restorative materials such as bisphenol A has been capable of production of DNA adducts via comet assay in different human cells in vitro [74, 75]. Exposure of experimental animals to methyl methacrylate has increased the number of micro-nucleated cells in bone marrow resulting in mutagenicity *in vivo* [76]. The latter can also produce DNA strand breaks in a dose dependent manner in

murine macrophages [77]. The protective role of antioxidants such as melatonin in reduction of the aforementioned genetic damages suggests the pivotal role of oxidative hazard in the mechanism of genotoxicity of dental materials [78, 79]. Endodontics compounds have also been the subject of extensive studies in the context of genotoxicity in several in vitro experiments. However, more reliable usage and clinical tests will provide a roadmap for future dentistry.

Screening Methods

Selection of biocompatible materials adoptable with pulp and other live tissues with minimal cytotoxic effects is an important issue in dentistry and medicine. Possessing no or very few deleterious effects on oral tissue is the definition of biocompatible dental material.

Dental materials must be assessed through several toxicity and biocompatibility steps before they could be used in clinic. Figure 1 illustrated the example of these tests at three steps. Biocompatibility assays will pinpoint the detrimental effects of materials, estimate the dose of chemicals released and survey the reactions to this dose.

The first step for evaluation of dental materials as in other chemicals is *in vitro* cytotoxicity tests. In addition to usual cell viability assays there are some special terms in biocompatibility screening of dental materials. As mentioned in figure 1, in *in vitro* tests direct or indirect contact between cells and dental materials define direct and/or indirect cell contact tests in which a barrier is the determinant factors [80].

In agar diffusion test, the test material is basically incubated on a layer of agar covering a monolayer cell culture where the diffusion of the substance through agar is used to determine the non-specific cytotoxicity of materials [81]. In similar techniques Millipore filter is the surrogate of the agarose. However these two methods may not be the ideal test for imitating the oral environment. Dentin barrier tests via stimulating the *in vivo* oral cavity environment makes it a preferable cytotoxicity assay [82].

In the next step, biological analysis depend on animal experimentation to a great extent. Before a dental material can be utilized in practice, it must always be assessed comprehensively in several species of laboratory animals to establish its local and systemic impact in the body [83]. Moreover, *in vivo* tests help to anticipate the potential toxic risks that might be encountered in man. Some of these test have been mentioned in figure 2.

Finally, the ideal methodology for biocompatibility evaluation is clinical tests in individuals. However, ethical and legal consideration may restrict this approach. Figure 2.

Conclusion

It is essential to use healthy and safe materials medical approaches. In dentistry, application of different material in long-term oral usage demands low or non-toxic agents gains importance for both patients and the staff. Furthermore, screening tests should evaluate any potential toxicity before clinical application.

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Conflict of Interest

The authors declare that there are no conflicts of interest associated with this work.

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Figure legends:

Tables

Table 1 Major symptoms observed after exposure to hydrofluoric acid and the first aid measures.

Classification of dental used materials based on biocompatibility [84, 85]

Table 2 Classification of dental used materials based on biocompatibility [84, 85]

Figures

Figure 1. Mercury induced cytotoxicity and related signaling pathways. Mercury is the main component of amalgam used to fill cavities in dentistry. It induces of different signaling pathways leading to cell death, DNA damage and liver dysfunction.

Figure2. Different steps in evaluation of the toxicity and biocompatibility of dental materials.

Tables:

Biocompatibility class	Definition in dentistry	Examples of dental used materials	The main characteristic in related to bone
Biotolerant	Materials that are separated from bone tissue by a layer of fibrous tissue.	Cements based on poly (methyl methacrylate), stainless steels, Co alloys	Distance osteogenesis
Bioinert	Materials that possess the property of establishing chemical bonds with bone tissue (osseointegration).	Titanium, zirconium, aluminum, carbon	Direct contact to bony tissue, direct contact to osteogenesis
Bioactive	Materials may show direct contact with the adjacent bone tissue without chemical reactions between the implant and the tissue.	Hydroxy apatite, calcium carbonate, calcium phosphate, glass ceramics	Bonding to bony tissue, bonding osteogenesis

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Figure 1. Mercury induced cytotoxicity and related signaling pathways. Mercury is the main component of amalgam used to fill cavities in dentistry. It induces of different signaling pathways leading to cell death, DNA damage and liver dysfunction.

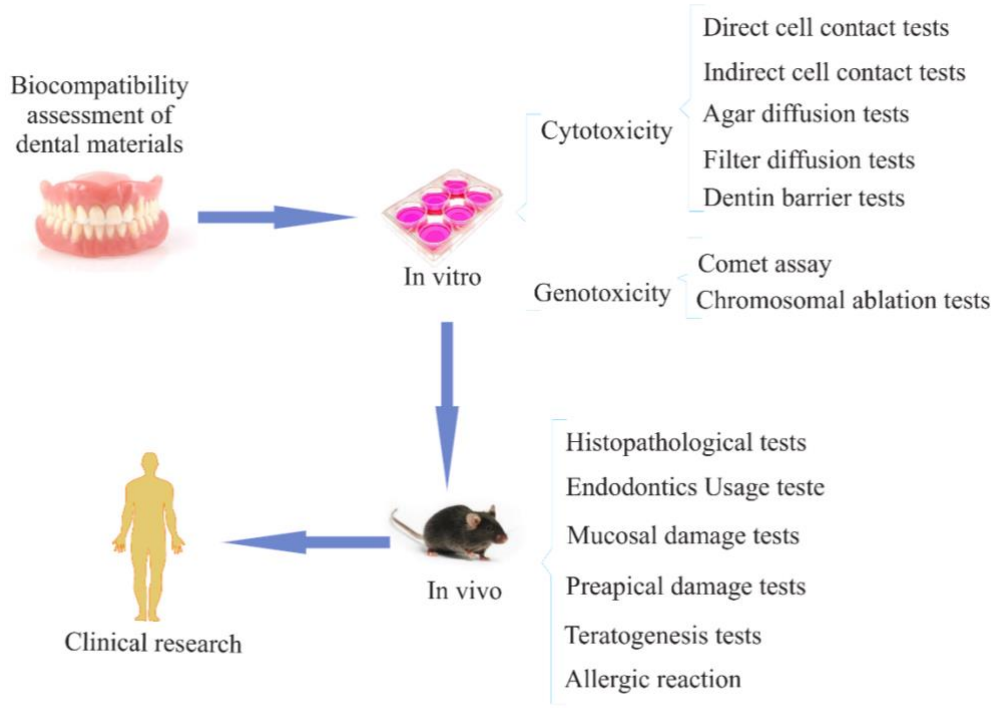

Figure 2. Different steps in evaluation of the toxicity and biocompatibility of dental materials.